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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/713,136	TUCK ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-42,63,65-86,88,89,95-97,99-101 and 106-108* is/are pending in the application.

4a) Of the above claim(s) *11-42,65-70,73,76-82,85,88 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63, 71-72, 74-75, 83-84, 86, 95-97, 99-101 and 106-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11-42, 63, 65-86, 88-89, 95-97, 99-101 and 106-108 are pending.

2. Claims 11-42, 65-70, 73, 76-82, 85, and 88-89 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 4/18/05, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 63, 71-72, 74-75, 83-84, 86, 95-97, 99-101 and 106-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and a polynucleotide wherein the polynucleotide consisting of an immunostimulatory sequence (ISS) selected from the group consisting of SEQ ID NO: 1-8 wherein the extent of conjugation in the population provides an average of at least 5.5 immunostimulatory sequence per antigen molecule, (2) The said population wherein the immunostimulatory sequence consisting of the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3', (3) the said population wherein the immunostimulatory sequence consisting of a sequence such as the ones set forth in claim 72, (4) a population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and a polynucleotide wherein the polynucleotide consisting of an immunostimulatory sequence (ISS) selected from the group consisting of SEQ ID NO: 1-8 wherein the extent of conjugation in the population provides a ratio of (i) average mass of ISS to (ii) average mass of antigen of at least about 45 to about 40, (5) the population of conjugate molecules, said molecules comprising a ragweed pollen allergen Amb a1 and an immunostimulatory sequence (ISS) consisting of the sequence selected from the group consisting of SEQ ID NO: 1-8, wherein the extent of conjugation in the population in the population provides a ratio of (i) average mass of ISS to (ii) average mass of antigen of at least about 45 to about 40 wherein the ISS consisting of the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3' or a sequence such as the ones

set forth in claim 84, (6) a composition comprising the population mentioned above in a pharmaceutically acceptable excipient, and (7) a population of conjugate molecules made by the process comprising: combining a polynucleotide consisting of an immunostimulatory sequence (ISS) of SEQ ID NO: 1 and an allergen at a ratio of about 17 molar equivalents of the polynucleotide to about 1 molar equivalent of the allergen whereby conjugate molecules comprising the polynucleotide and allergen are formed, wherein the polynucleotide is consisting of the sequence 5'-cytosine, guanine-3' for treating allergy, **does not** reasonably provide enablement for (1) *all* polynucleotide "comprising" any immunostimulatory sequence (ISS) comprises the sequence 5'cytosine, guanine-3' wherein polynucleotide is "greater than 8 and less than about 200 nucleotides in length" conjugated to the any antigen in the claimed population of conjugate molecules as set forth in claims 63, 75, and 108, (2) any ISS "comprises" the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine, C,G-3' (claims 71 and 83), (3) any ISS comprises any sequence (claims 72 and 84), (4) any "mammal allergen" as set forth in claims 96 and 100, (5) any antigen is any polypeptide as set forth in claims 106 and 107 in the claimed population of conjugate molecules or composition comprising said conjugates molecules as set forth in claims 63, 71-72, 74-75, 83-84, 86, and 94-101, and 106-108. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only eight specific immunostimulatory sequences (ISS) consisting of the nucleotide sequence selected from the group consisting of SEQ ID NO: 1-8. The specification discloses only one ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1 (See page 71). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L

(4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses the term "antigen" means any substance such as peptides, proteins, glycoproteins, polysaccharides, complex carbohydrates, sugars, gangliosides lipids, and phospholipids; portions thereof and combination thereof (page 16, lines 20-22). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14). The specification defines the term "polynucleotide" and "oligonucleotide" include single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA), modified oligonucleotides and oligonucleotides or combination thereof.

The specification does not teach how to make any population of conjugate molecules mentioned above because the term "comprising" or "comprises" is open-ended. It expands the immunostimulatory sequence (ISS) to include additional undisclosed nucleotides at either or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine. In addition to the problem of the undisclosed ISS, there is insufficient guidance as to the structure of the polynucleotide that is "greater than 8 and less than about 200 nucleotides in length" without the nucleotide sequence. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS consisting of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotide containing the ISS is not adequate taught in the specification without the nucleotide sequence. Further, there is insufficient guidance as to the structure of any "mammal allergen" without the amino acid sequence.

Stryer *et al,* of record, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al,* of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Chatel et al, of record, teach various factors such as allergen structure, mouse strain, CpG/recombinant protein expression influence the immune response (see entire document, abstract, in particular). Without the structure of the allergen such as "mammal allergen" and the

polynucleotide comprising any ISS sequence, it is unpredictable which undisclosed "mammal allergen" unconjugated to which undisclosed polynucleotide has stimulatory activity.

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Segal *et al*, of record, teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant that triggering *autoimmune disease* in predisposed susceptible individual (See abstract, in particular).

Yamada *et al*, of record, teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Yamada et al teach oligonucleotides containing runs of greater than 15 polyGs can inhibit both CpG and mitogen induced immune response (see page 5593, col. 2, second full paragraph, in particular). Yamada *et al* also teach the relative locations of the immunostimulatory motif such as CG on a DNA strand determine the magnitude and nature of the resultant immune response and suppression is generally dominant over stimulation. However, when a CpG motif is immediately 5' to a suppressive motif, stimulation dominates. Further, when the distance between motifs exceeds 10 bases, this effect dissipates (see page 5594, first paragraph, in particular). Given the unlimited number of polynucleotide "comprising" an ISS conjugated to unlimited number of allergen such as mammal allergen, there is insufficient working examples demonstrating that the undisclosed population of conjugate molecules are immunostimulatory, let alone in vivo working example that population of conjugate molecules are useful for treating allergy.

Without the structure of the allergen and the polynucleotide, one skill in the art cannot make, much less use the claimed invention. Since the allergen such as mammal allergen and polynucleotide in the conjugate molecules are not enabled, it follows that the composition comprising the undisclosed population of conjugate molecules in a pharmaceutically acceptable carrier is not enabled. It also follows that the mass of the ISS containing polynucleotide and the mass of the antigen cannot be determined without the nucleotide and amino acid sequences, respectively. Since the molecule weight of the antigen depends upon the amino acid sequence, without the amino acid sequence of the antigen, the molecular weight of the antigen cannot be determined. Likewise, the molecule weight of the polynucleotide comprising ISS depends on the

nucleotide sequence, such double strand or single- stranded deoxyribonucleotide, single-stranded RNA, the length of such nucleotide. Without the information about the nucleotide sequence, one skill in the art cannot determine the molecular weight, in turn the desired concentration of the molar ratio of the conjugate molecule.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 4/18/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claimed invention is directed to ISS which comprises "5'cytosine guanine-3'. The term "5'-cytosine guanine-3'" indicates that the ISS includes a CG dinucleotide in which the C is to the 5' side of the G and the G is to the 3' side of the C. All the exemplary ISS listed on page 36-38 of the specification contain a CG dinucleotide and none of them contain a C on the 5' end of the oligonucleotide and a G on the '3' end of the oligonucleotide. (2) allergens for use in the claimed invention are well known in the art. (3) Polynucleotides greater than 8 and less than about 200 nucleotides in length comprising an ISS wherein the ISS comprises a CG dinucleotide, are also well known in the art. The invention lies in the unique combination of resultant activity of the ISS-allergen conjugate molecules prepared according to the instant specification.

In response to applicant's argument that term "5'-cytosine guanine-3'" is referring to the CG dinucleotide, the term "dinucleotide" is not recited in the claims. Further, the term "5'-cytosine guanine-3'" could be any oligonucleotide greater than 8 and less than about 200 nucleotides in length so long the 5' end of the oligonucleotide is cytosine and the 3' end is guanine.

In contrast to applicant's argument that polynucleotide greater than 8 and less than about 200 nucleotides in length comprising an ISS wherein the ISS comprises a CG dinucleotide, are

also well known in the art, the term "comprises" is open-ended. It expands the CG dinucleotide to include additional nucleotides at either or both ends so long the polynucleotide is greater than 8 and less than about 200 nucleotides in length. The specification defines the term "polynucleotide" and "oligonucleotide" include single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA), modified oligonucleotides and oligonucleotides or combination thereof. There is insufficient guidance as to which nucleotides to be added without the nucleotide sequence, let alone the "polynucleotide" is any single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA), modified oligonucleotides and oligonucleotides or combination thereof conjugated to any allergen. There is a lack of disclosure as to whether the undisclosed polynucleotide when conjugated to any allergen has the same immunostimulatory function for treating allergy. Without the information about the polynucleotide, one skill in the art cannot determine the molecular weight, in turn the desired concentration of the molar ratio of the conjugate molecule.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Van Uden *et al* (PTO 1449) teach even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood (See page 903, in particular).

Segal *et al*, of record, teach that immunostimulatory sequences such as CpG oligonucleotides are potent adjuvant that triggering *autoimmune disease* in predisposed susceptible individual (See abstract, in particular).

Yamada *et al*, of record, teach that the sequence and length of a DNA strand determine its activity and depending on how these polynucleotide's secondary/tertiary structure are fold, activity may be gained or lost (See page 5593, column 2, second full paragraph, in particular). Yamada et al teach oligonucleotides containing runs of greater than 15 polyGs can inhibit both CpG and mitogen induced immune response (see page 5593, col. 2, second full paragraph, in particular). Yamada *et al* also teach the relative locations of the immunostimulatory motif such as CG on a DNA strand determine the magnitude and nature of the resultant immune response and suppression is generally dominant over stimulation. However, when a CpG motif is immediately 5' to a suppressive motif, stimulation dominates. However, when the distance

between motifs exceeds 10 bases, this effect dissipates (see page 5594, first paragraph, in particular). Given the unlimited number of polynucleotide "comprising" an ISS conjugated to unlimited number of allergen such as mammal allergen, there is insufficient working examples demonstrating that the undisclosed population of conjugate molecules are immunostimulatory, let alone in vivo working example that population of conjugate molecules are useful for treating allergy.

In contrast to applicant's argument that allergens are known in the art, the specification does not teach any and all allergen such as "mammal allergen", the specification discloses only the specific Fel dI from cat, Bos d2 from Cow, Can fI and Can f2 from dog, Equ c1 from horse, and mouse urinary protein from mouse (see Table 1, page 45), the specification does not teach all mammal allergen such as allergen from whale, and any allergen from all insects, all pollen, all nut, all crustacean and all fungal allergen.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Chatel et al teach various factors such as allergen structure, mouse strain, CpG/recombinant protein expression influence the immune response (see entire document, abstract, in particular). Without the structure of the allergen such as "mammal allergen" and the polynucleotide comprising any ISS sequence, it is unpredictable which undisclosed "mammal allergen" unconjugated to which undisclosed polynucleotide has stimulatory activity. Without the structure of the allergen and the polynucleotide, one skill in the art cannot make, much less use the claimed invention.

6. Claims 63, 71-72, 74-75, 83-84, 86, 95-97, 99-101 and 106-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* polynucleotide comprising any immunostimulatory sequence (ISS) comprises the sequence 5'cytosine, guanine-3' wherein polynucleotide is greater than 8 and less than about 200 nucleotides in length conjugated to the any antigen in the claimed population of conjugate

molecules as set forth in claims 63, 75, and 108, (2) any ISS "comprises" the sequence 5'-purine, purine, C,G, pyrimidine, pyrimidine, C,G-3' (claims 71 and 83), (3) any ISS comprises any sequence (claims 72 and 84), (4) any "allergen" as set forth in claims 63 and 75, (5) any "mammal allergen" as set forth in claims 96 and 100, (5) any allergen is any polypeptide as set forth in claims 106 and 107 in the claimed population of conjugate molecules or composition comprising said conjugates molecules as set forth in claims 63, 71-72, 74-75, 83-84, 86, 94-101 and 106-108.

The specification discloses only eight specific immunostimulatory sequences (ISS) consisting of a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-8. The specification discloses only one ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1 (See page 71). The conjugate was prepared by incubation of a mixture of ISS at various molar concentrations such as 4, 7 or 17 molar to 1 molar concentration of Amb a1. The antibody response and histamine release from various conjugates such as AIC-L (4:1), AIC-M (7:1) and AIC-H (17-1) are measured. The AIC-H (17-1) conjugate shift the Th2 to Th1 immune response as determined by IFNγ, IL-5 levels and histamine release (page 80-82). The specification discloses that the term "allergen" means antigen, or antigenic portion thereof of any molecule, usually a protein (see 18, lines 12-14) and allergen discloses in Table 1.

With the exception of the specific population of conjugates comprising the specific immunostimulatory sequence (ISS) and the specific allergen disclosed in Table 1, there is inadequate written description about the structure associated with function of all polynucleotide comprising any immunostimulatory sequence (ISS) wherein the polynucleotide is greater than 8 and less than about 200 nucleotide in the claimed conjugate molecules without the nucleotide sequence. Further the term "comprising" is open-ended. It expands the polynucleotide to include additional nucleotides at either or both ends. Likewise, there is adequate written description for all ISS comprises the sequence 5'cytosine, guanine-3', all ISS such as the ones recited in claims 72 and 84 because the term "comprises" is open-ended. It expands the ISS in the conjugated molecules to include additional nucleotides at either or both ends. There is inadequate written about the nucleotides to be include at either or both ends. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotide containing the ISS is not adequate described without the nucleotide sequence.

With regard to "allergen" such as any "mammal allergen" in the population of conjugated molecules, there is insufficient written description about the "mammal allergen" without the

amino acid sequence. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification as-filed does not provide adequate written description support for "mammal allergen" other than the specific allergen disclosed in Table 1. Therefore, the skilled artisan can envision neither all the contemplated amino acid sequence of all allergen such as all mammal allergen, polypeptide antigen, nor the function of any mammal allergen. Consequently, conception in either case cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Further, the specification discloses only *one* ragweed allergen Amb a1 conjugated to a polynucleotide consisting of SEQ ID NO: 1. Given the lack of a written description of *any* additional representative species of population of conjugate molecules wherein the molecule comprises any allergen such as any mammal allergen, any polypeptide and any polynucleotide comprising any ISS wherein the polynucleotide is less than about 200 nucleotides in length, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Since the antigen or mammal allergen and polynucleotide in the conjugate molecules are not adequately described, it follows that the composition comprising the undisclosed population of conjugate molecules in a pharmaceutically acceptable carrier is not adequately described.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 4/18/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention involves the use of an ISS which relies on the presence of the 5'-CG-3' dinucleotide for activity. Many sequences which include the 5'-CG-3' sequence as well as additional nucleotide bases are known to provide immunostimulatory activity to the ISS-containing polynucleotide. (2) As amended, claims 63, 75 and 108 are directed to a population of conjugate molecules involving an allergen. The specification lists many examples in the specification, specific information for the allergens, including structural information was well known in the art at the time the application was filed. See, for example, the allergens and citations listed in Table 1, pages 44-47.

In response, the specification does not provide any written description about any polynucleotide "comprising" any immunostimulatory sequence (ISS) wherein said ISS "comprises" 5'cytosine, guanine-3' wherein the polynucleotide is greater than 8 and less than about 200 nucleotides in length conjugated to any allergen such as any "mammal allergen", any pollen allergen, any insect allergen, any nut allergen, any crustacean allergen and any fungal allergen. There is inadequate written description about the structure associated with function of all polynucleotide comprising any immunostimulatory sequence (ISS) "comprises" 5'Cytosine, guanine-3' wherein the polynucleotide is greater than 8 and less than about 200 nucleotide in the claimed conjugate molecules without the nucleotide sequence. Further the terms "comprising" and "comprises" are open-ended. It expands the polynucleotide and the ISS to include additional nucleotides at either or both ends. Likewise, there is adequate written description for all ISS comprises the sequence 5'cytosine, guanine-3', all ISS such as the ones recited in claims 72 and 84 because the term "comprises" is open-ended. It expands the ISS in the conjugated molecules to include additional nucleotides at either or both ends. There is inadequate written about the nucleotides to be include at either or both ends. Even if the ISS is limited to SEQ ID NO: 1, the specification discloses ISS of SEQ ID NO: 1 is only 22 nucleotides in length. The rest of polynucleotide that is less than 200 nucleotides in length is not adequate described without the nucleotide sequence.

With regard to "allergen" such as any "mammal allergen" in the population of conjugated molecules, there is insufficient written description about the mammal allergen without the amino acid sequence. Other than the specific population of conjugates comprising the specific immunostimulatory sequence (ISS) and the specific allergen disclosed in Table 1, there is

inadequate written description about the structure associated with function of all population of conjugate molecules.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 71, 83, 96 and 100 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "5'purine" in claim 71 has no antecedent basis in base claim 63 because "purine" consists of A or G. However, the amended claim 63 requires that the ISS comprises 5' cytosine (C), which is a pyrimidine.

The "5'purine" in claim 83 has no antecedent basis in base claim 75 because "5'-purine" consists of A or G. However, the amended claim 75 requires that the ISS begins with 5' cytosine (C), which is a pyrimidine.

The "mammal allergen" in claims 96 and 100 is ambiguous and indefinite because it is not clear which mammal the allergen belongs.

Applicants' arguments filed 4/18/05 have been fully considered but are not found persuasive.

Applicants' position is that (1) applicants maintain that the Examiner's interpretation of the language of claims 63 and 75 is incorrect and inconsistent with that taught in the specification and in the art. The specification makes clear that the phrase "ISS comprises the sequence 5'-cytosine, guanine-3' is the same as "ISS comprises a CG dinucleotide" or "ISS comprises 5'cytosine guanine-3'.

In response to applicant's argument that term "5'-cytosine guanine-3'" is referring to the CG dinucleotide, the term "dinucleotide" is not recited in the claims. Further, the term "5'-cytosine guanine-3'" could be any oligonucleotide greater than 8 and less than about 200 nucleotides in length so long the 5' end of the oligonucleotide is cytosine and the 3' end is guanine. Finally, dependent Claims 71, 83, 96 and 100 fail to further limit the subject matter of a previous claim, see 37 CFR 1.75(c).

9. Claim 108 stands free of prior art.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

13. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 8, 2005

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